Mutation Linked to Some Cases of Parkinson's

Identifying gene raises ethical questions about its use in testing, given the lack of preventive therapy.

BY CHRISTINE KILGORE
Contributing Writer

Screening for a recently identified mutation shown to cause approximately 5%-6% of familial and 1%-2% of apparently sporadic cases of Parkinson's disease will likely become an important component of genetic testing and counseling for this disease, according to investigators involved in the research.

"No other single mutation identified so far … has occurred with such high frequency" in patients with Parkinson's disease, said William C. Nichols, Ph.D., of Cincinnati Children's Hospital Medical Center, and his associates. Their report was one of three on the mutation published online in the Lancet.

However, two issues need to be resolved before genetic testing for Parkinson's disease can fulfill its potential, Dr. Nichols told this newspaper.

"First, there is nothing which can be done for patients carrying the genetic mutation and thus might be predisposed to developing Parkinson's disease. And … [w]e can't yet predict what an individual's chances of developing the disease are, given they carry a predisposing mutation," he said.

The new research reported in the Lancet builds on findings published last year showing that mutations in the gene termed *LRRK2* (for leucine-rich repeat kinase 2) cause some forms of autosomal dominant Parkinson's disease (Neuron 2004;44:601-7).

The gene codes for the protein dardarin, which is the first kinase to be implicated in the disease.

In research completed since then, a specific mutation in the *LRRK2* gene, Gly2019Ser, was identified in several families. The investigators of the just-published studies sought to investigate the frequency of this mutation and its role in susceptibility to Parkinson's disease.

Dr. Nichols and his colleagues analyzed 358 North American families with at least one pair of siblings with Parkinson's disease. They found that 35 of 767 affected members of these families (5%)—in 20 of the 358 families—had at least one copy of the mutated gene.

One of these 35 patients was homozygous for the mutation, they reported (Lancet 2005;365:410-2).

Alessio Di Fonzo, M.D., of the University of Milan, and his colleagues, also detected the mutation in 4 of 61 families (7%) with Parkinson's disease and apparent autosomal dominant inheritance. The families were from Italy, Portugal, and Brazil (Lancet 2005;365:412-5).

And William P. Gilks, of the Institute of Neurology and National Hospital for Neurology and Neurosurgery in London, and his associates, detected heterozygous Gly2019Ser mutations in 8 (2%) of 482 apparently sporadic cases, predominantly from the southeast of England.

Three of the patients turned out to have positive family histories (two involved first-degree relatives, and one involved a second-degree relative), Mr. Gilks and his colleagues reported (Lancet 2005;365:415-6).

Each of the studies included large control populations; the mutation was absent from all the control populations tested.

Alexis Brice, M.D., who commented on the studies in the same issue of the Lancet, called identification of the Gly2019Ser mutation "a major advance." The mutation "accounts for a surprisingly high proportion of both familial and isolated cases (of the disease)," he said.

Still, there is much to learn, he said. Patients with the Gly2019Ser mutation have typical clinical features of Parkinson's disease, for instance, but the associated clinical spectrum "must be better established," he said.

Pathologic markers also must be better understood; the neuropathology in patients with the mutations—for instance, the extent and type of Lewy bodies—appears to vary considerably, even within the same family, noted Dr. Brice of Université Pierre et Marie Curie in Paris (Lancet 2005;365:363-4).

He and the investigators also cited the need to know more about the precise penetrance of the mutation before the new results are translated into practice.

In addition to Dr. Gilks' finding of the mutation in patients without any family history of Parkinson's disease, Dr. Nichols found that "despite the apparent autosomal dominant effect (of the mutation)," only 13 (37%) of the siblings with a mutation reported having a parent with Parkinson's disease.

Dr. Di Fonzo and his colleagues also identified some asymptomatic carriers—a finding that suggests penetrance was reduced or was age dependent.

Dr. Nichols, moreover, pointed out that, in his study, carriers of the mutation also had less severe clinical symptoms despite having had the disease for a longer time, which suggests that "the mutation is associated with slowed disease progression," he said.

Despite the unanswered questions, now that the Gly2019Ser mutation has been identified, "there will be requests for presymptomatic testing by offspring of carriers," Dr. Brice said in his commentary.

This "raises ethical issues similar to those for Huntington's disease" since, without a preventive treatment, "testing offers no direct medical benefit," he pointed out.

Dr. Nichols, in his remarks to this newspaper, noted: "I would not be surprised if there were not some company that will soon offer genetic testing for Parkinson's disease, maybe even at the prenatal level, because people are willing to pay for it."

Dr. Brice noted that identification of the gene and the mutation should lead to a better understanding of the pathologic mechanism underlying Parkinson's disease, which will "hopefully lead to new treatments," he said. "The last page on the genetic basis of Parkinson's disease is yet to be written, and it promises to be very exciting." ■

New Findings Improve Counseling for Epilepsy Surgery

BY BRUCE JANCIN
Denver Bureau

Breckenridge, Colo. — Recent research has enabled physicians to counsel patients with drug-refractory temporal lobe epilepsy much more effectively about the risks and benefits of resective surgery, Lauren C. Frey, M.D., said at a conference on epilepsy syndromes sponsored by the University of Texas at San Antonio.

Moreover, there are now data that for the first time begin to address the impact of withholding surgery in such patients, said Dr. Frey, a neurologist at the University of Colorado, Denver.

These studies demonstrate that continued, poorly controlled and chronic seizures are associated with increased rates of cognitive decline, impaired quality of life, injury, and even sudden death.

In one recent study, investigators at the University of Göteborg (Sweden) performed formal neuropsychologic testing in 36 adults with a mean age in their early 30s who had long-time, drug-resistant partial epilepsy and in a healthy control group matched for age, gender, and education level. Cognition at baseline was worse in patients with intractable epilepsy than controls. At follow-up testing nearly 5 years later, patients showed further significant declines in general cognition and verbal memory (Epilepsy Behav. 2004;5:677-86).

Conference director José E. Cavazos, M.D., observed that sudden unexpected death in epilepsy patients (SUDEP) is another important issue to raise in counseling patients about the risks and benefits of epilepsy surgery.

Continued, poorly controlled seizures are associated with increased rates of cognitive decline.

DR. FREY

Studies suggest the incidence of SUDEP is 1 in 200 per year among patients with intractable epilepsy, and that this risk is erased in those whose seizures become well controlled, said Dr. Cavazos of the South Texas Comprehensive Epilepsy Center at the University of Texas at San Antonio.

In a typical year, SUDEP claims two or three lives among adults seen at the center who decline surgery for drug-refractory epilepsy, Dr. Cavazos added.

Dr. Frey said that probably the best study to date addressing mental decline in patients with uncontrolled epilepsy involved 147 adults with a mean age in their early 30s at baseline with surgically and 102 with medically managed temporal lobe epilepsy evaluated longitudinally at the University of Bonn (Germany).

Neuropsychologic testing conducted at baseline and at 1, 2, and 10 years' follow-up showed progressive cognitive deterioration, particularly in memory function, in those patients whose seizures continued despite surgery or medical management. Surgery, whether successful or not, caused cognitive deficits in the short run, but the deficits were often reversed in patients who became seizure free (Ann. Neurol. 2003;54:425-32).

This study highlights the dichotomous nature of epilepsy surgery outcomes. Many patients are double winners: They become seizure free, with a resultant halt in the long-term cognitive decline associated with chronic seizures as well as the potential for reversal of the deficits caused by surgery. But a smaller number of patients are double losers: They experience continued seizures resulting in progressive cognitive deterioration as well as acceleration of the deficits associated with the surgery.

A landmark randomized controlled trial of surgery for drug-refractory temporal lobe epilepsy (80 patients) showed 58% of surgically treated patients were free of seizures impairing consciousness at 1 year, compared with 8% of medically treated patients. Also, 38% of surgically and 3% of medically treated patients were completely seizure free. The surgical group scored significantly better on the Quality Of Life In Epilepsy-89 (QOLIE-89) and showed trends for higher rates of employment and school attendance. Participants had a mean age in their early to mid 30s.

Twenty-two surgically treated patients had subtle visual field deficits of which they were unaware, while two experienced a decline in verbal memory that interfered with their work performance (N. Engl. J. Med. 2001;345:311-5).

Other studies have shown that this surgically related verbal memory impairment doesn't improve over time and can have a significant quality of life impact.

Risk factors identified for this verbal memory decline include later age of epilepsy onset, higher memory performance at baseline, dominant hemisphere resection, no clear asymmetry of memory function during testing, and an absence of clear structural abnormalities of the mesial temporal structures on the side being considered for resection. ■